DETAILED ACTION

Response to Amendment

1. Claims 1-71 have been cancelled and new claims 72-100 have been added as requested in the amendment filed on March 24, 2008. In the Response to Restriction/Election filed October 4, 2007, Applicant has elected the invention of Group 10 drawn to a method of treatment using an antibody directed toward the sequence of SEQ ID NO: 1. Following the amendment, claims 72-100 are pending and, in so far as they read upon the elected subject matter, are under examination in the instant office action.

2. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

3. Applicant's arguments filed on March 24, 2008 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Objections

4. Claims 73-80, 83, 85, 86, 90 and 94 are objected to because of the following informalities: Claims 73-80, 83, 85, 86, 90 and 94 are dependent from cancelled claims.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. As currently amended, Claims 72, 81, 82, 84, 87-89, 91-93 and 95-100 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, as applied to claims 1-5, 7, 10-17, 33-37, 40-42 and 45, for reasons of record in the Office Action mailed October 24, 2007. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is noted that the Application Number on page 1 of the Declaration filed March 24, 2008 is different from the application number of the instant patent application. The declaration of Dr. Thomas Willnow under 37 CFR 1.132 filed March 24, 2008 will be treated as if it was submitted with the instant application number, but is found to be insufficient to overcome the rejection of claims 72, 81, 82, 84, 87-89, 91-93 and 95-100 based upon 35 U.S.C. 112, first paragraph as set forth in the last Office action for the following reasons. While Examiner does not dispute Dr. Willnow's declarations of "the finding that the Vps10p-domain receptors of the present invention are the main receptors behind the death inducing capacity of proneurotrophins" (Declaration page 1) and that "pro-neurotrophins exert a pro-apoptotic effect" (page 5), this does not strictly correspond to the invention as instantly claimed. There is no evidence of record that provides a nexus between the pro-apoptotic effect of pro-neurotrophins and the etiology, pathology and symptomology of an injury or dysfunction of the central or peripheral nervous system. The references cited in the declaration in support of evidence of a specific role disease pathology (Lee et al. 2001; Mizuno et al. 1998; and

Solary et al. 1996). Indeed, in its conclusory statement, the Mizuno et al. and Solary et al. references stresses the need for further research on apoptosis for therapeutic strategies. These references do not provide evidence or guidance in support of the enablement requirement of 35 USC 112, first paragraph. Specifically, the prior art and the instant specification fail to provide guidance as to a method comprising the administration of any antibody raised against SEQ ID NO: 1 for use as a treatment of CNS or PNS injury or dysfunction. Lastly, the declaration argues that antibodies against SEQ ID NO: 1 are currently known in the art (Declaration, Table pages 13-17) and the methods of making and screening are routine enough in the art such that one of ordinary skill in the art would be able make and use an antibody as required by the claims (Declaration pages 18-19). While this has been fully considered it is not found persuasive for the following reasons.

The standard of an enabling disclosure is not the ability to make and test if the invention worked but one of the ability to make and use with a reasonable expectation of success. A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of *Genentec, Inc, v. Novo Nordisk*, 42 USPQ 2d 100,(CAFC 1997), the court held that:

> "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in

the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

Thus, the Declaration is insufficient to overcome the rejections because it does not provide a preponderance of evidence that the specification adequately describes the claimed subject matter in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 72, 81, 82, 84, 87-89, 91-93 and 95-100 are drawn to methods of treatment of an injury or dysfunction of the central or peripheral nervous system comprising administering an effective amount of an antibody inhibitor, wherein the antibody binds to any receptor of the Vps10p-domain receptor family thereby inhibiting the binding of a pro-neurotrophin to said receptor. The claims are broadly encompass methods for the treatment of any injury or dysfunction of the central or peripheral nervous system comprising administering any antibody to a Vsp10p-domain receptor and inhibiting the binding of any neurotrophin.

The invention is based on finding that modulation of the Vps10p-domain receptor family affects neurotrophin or pro-neurothrophin activity. However, the instant specification does not disclose any direct connection between Vps10p-domain receptors and neurotrophin or pro-neurothrophin activity, and therefore, is not found to be enabled for the method as claimed, for the following reasons. The instant specification does not provide evidence of a specific antibody that binds to a receptor of the Vps10p-domain receptor family, nor does it provide evidence that such binding mediates a physiological effect that is effective to treat any disease. The claims

encompass treatment of a vast array of injuries or dysfunctions of the central and/or peripheral nervous system, including treatment of hereditary disorders. For many of these dysfunctions or injuries there is no evidence of record that there is a nexus between Vsp10p-domain receptor function and disease etiology, pathology or symptomology. Thus, there is no evidence of record that inhibiting the binding between a receptor of the Vps10p-domain receptor family and a proneurotrophin would mediate a therapeutic effect, as claimed. Furthermore, the specification provides no guidance or working examples for methods of treating diseases or disorders comprising administering an antibody that binds to a receptor of the Vsp10p-domain receptor family, which would show that the claimed method was successfully achieved. Absent such guidance, one of ordinary skill in the art would require undue experimentation to discover how to practice Applicant's invention, as currently claimed.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

The nature of the invention relates to methods of treatment for *any* injury or dysfunction of the central or peripheral nervous system and the sole active step of the method comprises administering any antibody that binds to a receptor of the Vps10p-

domain receptor family and inhibits the binding between said receptor and a proneurotrophin.

On page 4 of the instant specification, Applicant states "some progress has been made as to an understanding of the role of this family [of receptors]". Examiner maintains, for reasons of record in the previous Office Action that, at the time of filing, the state of the art with respect to a function of these Vsp10-domain receptors was speculative at best.

While the skill level in the art is high, the level of predictability is low. While Examiner does not refute the clinical use of monoclonal antibodies, the specific examples cited in the Declaration, Rituxan, Remicade and Herceptin (page 19), are each highly engineered antibodies directed toward targeted epitopes, and their engineering and specificity are a testament to the unpredictability of any antibody to work therapeutically. The instant specification fails to identify even one antibody for treatment of CNS or PNS injury or dysfunction, and broadly claims that any antibody can be used with a reasonable expectation of success. Given the unpredictability within the field, the disclosure has not provided guidance as to how the invention may be practiced to the full scope of the claims.

The Pardridge reference in the previous office action was relied upon to demonstrate that even currently within the art, there remains much unpredictability for the use of antibodies as therapeutic treatments within the central nervous system. The reference particularly discusses the potential problems of antibody delivery across the blood brain barrier (BBB) and despite the construction of specifically engineered

chimera antibody-antibody fusion proteins (page 1739) problems of Ig transport across the BBB remain. The declaration suggests that this hurdle may be overcome by the administration of sortilin antibodies to patients with diseases that already demonstrate "leaky BBB" (page 20). While it is true that in conditions such as stroke the BBB may become "leaky", this finding does not overcome rejection because the disclosure is still lacking a show of enabling support with respect to the antibody of the claims and broad scope of the injuries and dysfunctions, as instantly claimed.

Furthermore, even if one circumvents the hurdles of BBB transport, the following current reference demonstrates that within the art there are very few therapeutically effective monoclonal antibodies that recognize intracellular antigens, and these are useful in oncotherapy only because the high rate of cell turn-over makes these intracellular antigens accessible within necrotic tissues (Shapiro et al., *Expert Opinion in Biological Therapy*, 6(5): 541-545, 2006).

With respect to claim breadth, the standard under 35 U.S.C. §112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. In addition, when analyzing the scope of enablement, the claims are analyzed with respect to the teachings of the specification and are to be given their broadest reasonable interpretation that is consistent with the specification. See MPEP 2111 [R-1], which states: "During patent examination, the pending claims must be "given *>their< broadest reasonable interpretation consistent with the specification." *In re Hyatt*, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). Applicant always has the opportunity to amend the claims during prosecution, and broad

interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. *In re Prater*, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550- 51 (CCPA 1969)".

As such, the broadest reasonable interpretation of the claimed method is that it allows for the treatment of *any* injury or dysfunction of the central or peripheral nervous system comprising administering *any* antibody that binds to any receptor of the "Vsp10p-domain" family (see also section 6 above) and inhibits the binding of any pro-neurotrophin (see also section 6). Thus, the claims encompass an unreasonable number of pathologically distinct conditions and disorders, many of which have no nexus or association at all to Vps10p-domain receptor and a skilled artisan would not know how to treat these diseases based solely on administration of an inhibitory antibody. As opposed to the claims, what is disclosed about the claimed method is narrow: There are no working examples of any specific antibody that is known to mediate such effects, and no guidance or direction as how to use the antibody in humans for treatment of any injury or dysfunction of the central or peripheral nervous system. The rejection is maintained for lack of evidence, guidance or direction within the disclosure as to how to make and use the invention to as claimed.

Conclusion

7. No Claim is allowed.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STACEY MACFARLANE whose telephone number is (571)270-3057. The examiner can normally be reached on M,W and ALT F 7 am to 3:30, T & R 5:30 -5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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